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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER: KRSEK, STAPLES, J

ART UNIT: 1813 | PAPER NUMBER: 10

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18N1/0912

DATE MAILED: 09/12/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on A and B 3-18-94 + C 6-20-94 A and B ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-2 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-2 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicant's amendments filed March 18, 1994 and June 20, 1994 have been entered. Claims 1 and 2 have been amended and are pending.

The error in the filing date stated in the previous Office Action is acknowledged. As noted by Applicant the statement should have read "...March 16, 1993 is considered to be the effective filing date of this application".

Applicant states that the reference on page 17 to another Application was an error and that the reference should be the issued patent number 4,976,957. This amendment to the specification has not been entered because it is not clear whether the disclosures of Patent 4,976,957 and Application 07/744,649 are identical and whether such a substitution would constitute new matter. Eight other applications are also improperly incorporated by reference on page 17 as stated in the previous Office Action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections which are Withdrawn

The rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph is withdrawn in view of the amendment of the claims.

The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Cantrell is withdrawn in view of the amendment of the claim.

The rejection of claim 1 under 35 U.S.C. § 102(e) as being anticipated by Rapp is withdrawn in view of the amendment of the claim.

Rejections which are Maintained

The objection to the specification and the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure is maintained for reasons of record.

The rejection of claims 1 and 2 under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks patentable utility is maintained for reasons of record. There was a typographical error in the previous Office action in that claims 1 and 3, rather than 1 and 2 were rejected, but claim 3 was withdrawn from consideration and the rejection was applied to the pending claims 1 and 2.

Response to Applicant's Arguments

Applicant argues that Example 2 of the specification teaches how to make malignin and a derivative of malignin. Applicant states that Examples 1 through 7 describe properties of

malignin and other Recogins as observed with reference to their specific antibody so that the chemical nature and properties of the vaccine are defined. Applicant argues that one can only claim to have a "vaccine" if there is evidence of its specific antibody or antibodies and that the properties in the examples in terms of generation of and reaction with the vaccine's specific antibody are critical to the concept of and definition of the vaccine. Applicant argues that Patent 4,976,957 describes the methods of preparing malignin and other Recognins and adds more detail on how to make the vaccine. Applicant states that Example 8 details the method of administering the vaccine. Applicant sets forth three lines of evidence that enhancement of antibody concentration would occur with "booster" doses of vaccine and that this increase in antibody concentration would result in improved survival of the cancer patient. Applicant states that these data by themselves did not compel the conclusion that a recognin vaccine might be useful but, when read in light of the findings in the specification where antibody increases in pre-cancer individuals as the cancer risk increases and that the antibody is cytotoxic to cancer cells, that a possibility of a vaccine is presented. Applicant argues that one of ordinary skill in the art could predict that the claimed vaccine would sufficiently increase the level of anti-Recognin antibodies to prevent or treat cancer in humans.

Applicant's arguments have been considered but are not deemed to be persuasive. Examiner agrees that the specification teaches how to purify malignin and that the specification describes properties of malignin and other Recogins as observed with reference to their specific antibody. The specification also discloses that malignin or recognins may be administered as a vaccine. Examiner also agrees that the administration of a vaccine results in the formation of

antibodies and that these antibodies may be used to further characterize the vaccine. However, as stated in the previous Office Action, the specification does not teach that Recognin, when administered as a vaccine, prevents or treats clinical cancer. Although the administration of the antigen *in vivo* results in an increased antibody response, a boost of antibody production also occurs *in vitro*, and patients with higher levels of anti-malignin antibodies have longer survival, this data does not demonstrate that the administration of a recognin vaccine results in the treatment or prevention of cancer. The statistical significance of the survival studies shows that there is a correlation between anti-recognin antibodies and survival. However it is not clear whether the antibodies themselves are capable of treating or preventing cancer or whether other factors may be involved. The cytotoxicity of the antibody to cancer cells *in vitro* is also not sufficient to demonstrate that the administration of the vaccine would result in the treatment of cancer because the cytotoxicity measured *in vitro* cannot be extrapolated to the treatment of tumors *in vivo* where other factors such as the anatomical location of the tumor, the tumor mass, and the long tumor-host relationship make the *in vitro* system much more complex and unpredictable. Therefore, it is maintained that one of ordinary skill in the art could not predict that the claimed vaccine would be effective in preventing or treating cancer in humans.

New Grounds of Rejection

Claims 1 and 2 are rejected under 35 U.S.C. § 103 as being unpatentable over Cantrell or Rapp in view of Bogoch et al (1980) and Bogoch et al (1991).

Cantrell teaches the administration of tumor associated antigens as vaccines to prevent or treat cancer (column 2, line 66 and column 7, lines 47 to column 8, line 5). Rapp teaches the administration of oncoproteins induce an anti-oncoprotein immune response to neutralize cancer (column 2, lines 10-23). Rapp et al also teaches that oncoproteins are often immunogenic in their natural host and their presence on tumor cells renders the antigen presenting cells susceptible to immune surveillance (column 1, lines 30-35). Neither Cantrell nor Rapp teach the use of Recognin as a cancer vaccine.

Bogoch et al (1980) teach that Recognin is a tumor associated antigen (p 409, paragraph 1). Bogoch et al (1991) teach that Recognin is an oncoprotein (column 1, paragraph 3). It would have been obvious to one of ordinary skill in the art to use Recognin as a vaccine to treat or prevent cancer because both tumor associated antigens and oncoproteins can be used as tumor vaccines, as taught by Cantrell and Rapp, and because Recognin is both a tumor associated protein and an oncoprotein, as taught by Bogoch et al, one of ordinary skill would expect that Recognin could also be administered to induce and anti-Recognin immune response to neutralize cancer.

Response to Applicant's Arguments

Applicant argues that although Cantrell uses the term vaccine, nowhere are data shown which indicate that what is injected acts like a vaccine by producing a specific antibody which kills cancer cells and that, in contrast, Applicant demonstrates an immunological reaction which involves anti-Recognin antibody. Applicant states that the "antigens" disclosed by Cantrell are

in no way antigens because their composition is not defined nor are they shown to produce antibodies. Applicant states that the endotoxin MPL is not an antigen but is an adjuvant. Applicant also argues the composition taught by Cantrell is not claimed to be applicable to all cancers. Applicant also argues that an immune mechanism is not demonstrated by Cantrell and that the anti-tumor effects may be due to thousands of potentially toxic substances. Applicant argues that the patent of Cantrell is not relevant since Cantrell does not teach anything about tumor "antigens" or tumor "vaccines".

Applicant argues that Rapp asserts that the oncoproteins may be used as immunogens but gives no evidence that an immune response has been observed. Applicant argues that the proper controls were not performed in the data presented by Rapp. Applicant argues that because the tumor associated substances disclosed by Cantrell or the oncoproteins disclosed by Rapp have not demonstrated the production of antibodies and therefore cannot be qualified as vaccines that neither is relevant to the present Application. Applicant argues that the fact that Bogoch et al (1980) and Bogoch et al (1991) teach that Recognin is a tumor associated antigen and an oncoprotein is irrelevant because it does not determine that Recognin is a vaccine. Applicant states that no other tumor marker or oncoproteins have the demonstrated immune properties that permit them to be assigned the function and role of vaccines. Applicant argues that since one of ordinary skill would not know that anti-malignin antibody is a cytotoxic antibody which increases in concentration in normal humans as the risk of cancer increases, they would not expect that Recognins could be vaccines any more than they would expect that other several dozen tumor

markers and oncoproteins which have not had defined the full range of immune (i.e. antigen-antibody) properties could function as vaccines.

Applicant's arguments have been considered but are not deemed to be persuasive. Applicant's arguments of the prior art all center on the definition of a tumor vaccine. The statements made by Applicant suggest that in order to define a material as a tumor vaccine, this material must produce an specific antibody response which is cytotoxic to cancer cells. Applicant argues that because the tumor associated substances and the oncoproteins used by Cantrell and Rapp have not been shown to result in the formation of antibodies, neither represents a cancer vaccine and therefore this art is not relevant. However, the contemporary knowledge in the art at the time the application was filed gives a broader definition to tumor vaccines. According to the prior art, in order for a tumor vaccine to be effective it must induce or ~~argument~~ argument immune responses to the tumor being treated. This immune response could be an antibody and/or a cellular response (See for example Bystryn et al p 88 column 1). Although antibody attack on tumor cells plays a role in some tumor vaccines, a cellular component may be the main mechanism of protection in other vaccines (see Stevenson et al (1992) p 87 column 2). Therefore, the definition of tumor vaccine is not limited to those vaccines in which the immune response induced by the vaccine is strictly an antibody response but may instead be a T cell-mediated response. Although Applicant argues an immune mechanism is not demonstrated by Cantrell and that the composition is not applicable to all cancers, Cantrell discloses on column 7, lines 52 through column 8 line 4 that the vaccines are capable of eliciting an immune response in the host and that the response will be enhanced by the adjuvants of the invention. Cantrell also lists many

types of cancers which may be treated. Similarly, Rapp discloses an anti-oncoprotein immune response to neutralize cancer (column 2, line 15). Because Cantrell teaches the use of tumor associated antigens as vaccines to prevent or treat cancer and Rapp teaches that the administration of oncoproteins induce an anti-oncoprotein immune response to neutralize cancer and the Bogoch references teach that Recognin is both a tumor associated antigen and an oncoprotein, it would have been obvious to one of ordinary skill in the art to use Recognin as a vaccine to treat or prevent cancer because one of ordinary skill would expect that Recognin could also be administered to induce and anti-Recognin immune response to neutralize cancer. One of ordinary skill would not necessarily need to have known that anti-malignin antibody is a cytotoxic antibody which increases in concentration as the risk of cancer increases in order to be motivated to use Recognins as a vaccine because the tumor vaccine is not limited to an antibody-mediated mechanism of action.

No claims are allowable.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN

THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Krsek-Staples whose telephone number is (703) 305-7556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 308-4227. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

JKS
Julie Krsek-Staples, Ph.D.
September 8, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180